REMARKS

By this Amendment, Claims 1, 5, 12 and 23 are amended. Claims 11 and 47 are cancelled. Claims 1, 3-10, 12-19, 21-35, 45, 46, 48 and 49 are pending in this Application. Support for the amendments can be found in the Specification, e.g., page 32, last two paragraphs and claims as filed, e.g., cancelled claims. No issue of new matter arises. Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the March 30, 2006 Office Action and allowance of all pending claims.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 3-19, 21-35 and 45-49 were rejected under 35 U.S.C. §112 , second paragraph, as allegedly being indefinite. The Office Action includes several numbered paragraphs setting forth these rejections. Applicants respectfully traverse these rejections in corresponding numbered paragraphs.

1. The Office Action alleges that the scope of claim 22 is unclear. Applicants respectfully traverse this rejection. The Office Action applies an "always" standard relating to what constitutes a CDK. For example, "Tau PK II" is cited as having been renamed CDK6. Multiple names for identical biomolecules are known in the art and raise no issue of indefiniteness. For example, vasopressin is also known as ADH. The Office Action fails to recognize the accepted meaning in the art that served as basis for the original naming as well as the alternate name. The Office Action by its own admission indicates that the meaning of "Tau PK II" and CDK6 is known. Thus no issue of indefiniteness arises in this regard.

Additionally the specification provides a clear definition at page 1, lines 24 and 25: "cyclin-dependent kinases (cdks)" and further discusses alternative nomenclature. Kinase activity is well understood in the art. Similarly a dependence on cyclin for the activity of certain kinases is also well-understood. As such no issue of indefiniteness is present. Reconsideration and withdrawal of this rejection are respectfully requested.

2. Claim 23 was alleged to be unclear. The Office Action indicates that the wording of the claim does not provide for inhibition of a complex, only the CDK component of the complex. Applicants respectfully traverse this rejection, but nevertheless amend the claim to recite inhibition of the complex. The complex is a multi-component complex that contains a CDK as the active component of the complex. The claim rightfully features inhibition of the activity component, that is the CDK and now also the complex. The complex *per se* has kinase activity stemming from activity of the CDK. Thus whether one characterizes the CDK or the complex as being inhibited, the same activity is inhibited. Thus no issue of new matter arises in the amended

claim. In view of this explanation reconsideration and withdrawal of this rejection are respectfully requested.

3. The Office Action stands by an assertion that cyclin D does not exist. In fact multiple cyclin Ds are recognized, e.g., D1, D2 and D3, as mentioned in the Office Action. The art clearly recognizes proper uses of the term "cyclin D". For example medterms.com provides the following description:

> **Cyclin D:** A family of three closely related proteins termed cyclin D1, D2 and D3 that are expressed in an overlapping redundant fashion in all proliferating cell types and collectively control the progression of cells through the cell cycle. Since the D-cyclins are essential to cell division, they may also be involved in cancer.

Google indicates over a quarter million hits for "cyclin D". Clearly there is such entity as understood in the art. However, as offered in the February 16, 2006 Reply claim 23 is amended to incorporate subject matter of claim 47, now canceled. Applicants believe that this amendment obviates the rejection. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

4. *Clarification requested.* The Office Action refers to page 5 structures. No structures are found on page 5 of the claims current at the time of the Office Action. Applicants in their attempt to be responsive treat the reference to page 5 as a reference to page 3. If this is not the intent of the Examiner, he is requested to clarify the basis of this rejection.

The Office Action indicates an understanding that nitrogen and carbon have different chemical properties. The skilled artisan understands such property differences. For example,, the number of electrons available for bonding differs for different atoms of the periodic table according to recognized groups of the table. The Office Action states: "A N atom requires three bonds". Applicants respectfully traverse this requirement as stated in the Office Action. In general, nitrogen is often characterized as having three bonds. But that is not always the case. For example, nitrous oxide, ammonia and nitrogen dioxide are characterized with four bonds on the nitrogen. In contrast, in nitric oxide the oxygen and nitrogen atoms each have two bonds.

The Office Action questions whether the term "nitrogen atom" was used when Applicants intended a nitro or amino group. Applicants reiterate and emphasize the distinction between the different prepositions "by" and "with" as used in the present application. "Substituted by" has the meaning that one replaces the other, in the sense that a substitute teacher replaces the regularly assigned teacher. "Substituted with" refers to substituents, that is, compounds that are present with the atom to which they are bound as substituents. This distinction is used consistently throughout the application and the appropriate meanings are apparent from the

chemicals substituted. For example if a carbon were substituted "with" a nitrogen the nitrogen would have to have bonds in addition to those to the carbon. If the carbon and nitrogen formed a cyano group, then the carbon would not have two remaining valence sites for ring binding. But the claim language does not say: "substituted with", the third line of text referenced above states: "substituted by a nitrogen atom". Thus the carbon atom is not present with the nitrogen in the ring. One or more nitrogen atoms resides where the carbon(s) of, for example, the benzene ring would have been thereby forming, e.g., a pyridine, a pyridazine, a pyrimidine, a pyrazine, a triazine, etc. The Office Action sets forth a requirement that that the wording be changed if Applicants intend that the carbon be actually replaced. The Office Action cites language found in the claim text at lines 3 and 4 of the same portion of page 3 text "each carbon of the aromatic ring may be independently substituted with an X substituent". See the Office Action at page 3, lines 4 and 3 from the bottom. Clearly the wording is different. "Substituted **by** a nitrogen atom", line 3, is clearly different from "substituted **with** an X substituent", line 4. Emphasis added. Applicants respectfully assert that the language is different and that no further change is properly required. Reconsideration and withdrawal of this rejection are respectfully requested.

5. The Office Action has maintained a rejection relating to =O substituents. The basis for maintaining the rejection rests on a theory that in order to bind an O to a ring C, two Hs must be replaced. This is not true. Each carbon in, for example, a benzene structure has four bonds, two required to maintain the ring structure, a delocalized or resonant bond and a bond to a H (or a substituent on a substituted ring). Thus each carbon of for example a benzene ring may bond an =O and remain in the ring structure simply by losing a H (or substituent) bond and replacing the delocalized or resonant bond with a bond to the oxygen. The previous reply explained how this species was found in equilibrium with hydroxyl substituted conjugated molecules or aromatics. Applicants stand by the observations in the art that such structures exist. Although no declaration is believed necessary, Applicants offer to provide one if the Examiner remains unconvinced. Since the =O is inherently present in certain circumstances, other language in the claim is deemed to cover this event. The oxo containing molecule would form tautomers featured in the claims. Accordingly, to advance prosecution and simplify issues should an appeal be necessary, Applicants have amended claim 1 above, without changing the scope, but not explicitly reciting "=O". Applicants respectfully submit that this aspect of the rejection is now obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

6. The term alkylene was objected to as used with saturated and unsaturated. Applicants have provided an amended claim set where the appropriate definition from the specification is

inserted into the claims to replace the language objected to. Reconsideration and withdrawal of this rejection are respectfully requested.

7. The term "heterocyclic" is objected to. The problem as stated in the Office Action is that "the rest of the ring is undefined". Applicants respectfully traverse this rejection. Claim 1, page 4, lines 5-7, stated: "**R4 and R5 taken together with the nitrogen to which they are attached, form a heterocyclic ring of three to seven atoms including the nitrogen atom**". *Emphasis added.* Thus, contrary to the allegation of the Office Action, the rest of the ring is defined. Reconsideration and withdrawal of this rejection are respectfully requested.

8. Claim 47 was rejected as not further limiting claim 23. As offered in the February 16, 2006 Reply claim 47 is canceled, its language having been inserted into claim 23. This rejection is thereby believed to be obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

9-11. Mixed type of neoplasm was alleged to be unclear, but was interpreted by the Office Action not to mean "a mixed neoplasm in the ordinary sense". Claim 11 is cancelled. Claim 5 is amended to qualify what is meant by "mixed type of neoplasm". Reconsideration and withdrawal of this rejection are respectfully requested.

12. The Office Action maintained the rejection relating to "phenyl". Applicants respectfully assert that paragraph 21 of the previous reply sufficiently addressed which phenyl was referenced. The phenyl referred to was the phenyl referenced above in the claim. As amended the claim is even more clear in this regard. The office action also objected to the reference to both unsubstituted and substituted phenyls in conjunction with "where phenyl is substituted" language. Applicants respectfully submit that the skilled artisan would have understood the language in reference to phenyl substituents to apply only when they were present. But to render moot the Examiner's objection, claim 1 is amended above to insert the phrase "when substituted" to indicate that the list of substituents does not apply when no substituents are present. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph: written description

Claim 12 was rejected under 35 U.S.C. §112, first paragraph as allegedly going beyond teachings of the original specification. Claim 12 is amended above to obviate this rejection. Support for the amendment can be found in the specification as filed, for example in the original claims 3 and 12. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph: enablement

Claims 3-22, 24-26 45, 46 and 49 were rejected under 35 U.S.C. §112, first paragraph as allegedly requiring undue experimentation to practice the claimed invention. Applicants gratefully acknowledge the Examiner's indication that claims 1, 21-23, 27-35, 47 and 48 are not subject to this rejection. Claim 20 was previously canceled and claim 11 is canceled herewith. Thus with respect to claims 11 and 20 reconsideration and withdrawal of the rejection is deemed proper. With respect to claims 3-10, 12-19, 21-22, 24-26, 45-46 and 49 Applicants respectfully traverse this rejection. The numbers below correspond to the numbers set forth in the March 30, 2006 Office Action.

General Background

The *Wands* opinion was cited in the Office Action as is used herein as a guide to compare the various factors with those of the present invention. *Wands* concluded:

> **Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention.**

Wands required millions if not billions of cells. Thus, outcomes were unpredictable because millions if not billions or more of antibodies were possible. Only very few working examples (4) were shown out of the many millions or billions possible. The majority sampled were non-working examples.

The Office Action at page 30 expressed a lack of understanding of Applicants response. See, e.g., page 30, penultimate paragraph. "Applicants (sic) response here is not entirely understood. . . ." Non-working or inoperative embodiments are discussed in the case law and deemed acceptable in the literal claim scope. Case law defining the scope of enablement allows some amount of inoperative embodiments, even when inoperative embodiments outnumber operative embodiments are tolerated and do not render a claim invalid. This topic is discussed below in reference to specific issues raised in rejection.

(1)(a) Scope of compounds. The Office Action indicates that the scope of the claims that includes the Ra variable and several X substituents covers a multitude of compounds. This is identified as a factor to be considered according to *Wands*. The Office Action while citing this number provides no basis what the relationship to undue experimentation might be. Numbers alone, even high numbers such as those encountered in *Wands*, by themselves are not indicative of undue experimentation. Applicants respectfully submit that the specification provides more than adequate guidance and teaching with respect to the various Ra variables. See e.g., the tabular data beginning at page 67. The Office Action has not cited any basis that the number of

possible embodiments would lead undue experimentation to practice the instantly claimed invention with any one or even several of the embodiments selected. Indeed, the specification, for example at pages 117-168, provides a multitude of data describing attributes and effects of various embodiments of Ra. Depending on the chosen Z, claim 1 recites different acceptable Ra embodiments. The -Z-Ra portion of the molecule is not the portion responsible for binding the CDK. This portion modifies the basicity of the N to which Z is attached and as embodied in the claims serves to minimize uptake of the compound by red blood cells. Similar molecules without the improvement provided by the –Z-Ra were not sufficiently active *in vivo* because rapid uptake by the red blood cells made the compound unavailable for the intended targets. With this guidance, undue experimentation cannot be properly deemed as implicated. The examples teach the skilled artisan the wide range of substituents that improve the bioavailablity. The CDK reactive portion is maintained in all examples. Thus at least this factor does not favor a Wands based rejection.

(b) Scope of Diseases Covered. From pages 7 to 20, the Office Action mentions and describes a large plurality of diseases, yet does not set forth any reason why administration of a compound of claim 1 would require undue experimentation. Regardless of the disease, administration can be accomplished without undue experimentation. Thus this factor fails to support a *Wands* based rejection.

With respect to apoptosis, Applicants respectfully submit that the Examiner is reading into the claim language wording that is not present: "but blocking apoptosis, period." Office Action page 20, three lines from the bottom. There is no requirement in the claim language that the blocking has to be complete blocking in all cells as apparently inferred from the Office Action.

(2) The nature of the invention and predictability in the art. Complexity of the animal system is cited, including a listing of growth factors. Three apoptotic mechanisms are mentioned. Besides a listing of normal and pathologic physiologic functions and discussion of several, there is no indication that practicing the instant claims would require undue experimentation. Though these comments are made there is no explanation of any relationship to undue experimentation, the test of whether an invention is enabled. The burden is on the Office to establish a *prima facie* support for any rejection. This burden is not met. Thus analysis focused on this factor fails to support a *Wands* based rejection.

(3) Direction or Guidance. The Office Action acknowledges a teaching of dosing from 0.02-1mg/kg/day. This range was criticized as being totally generic for the range of disorders. The Office Action notes that some anti-cancer drugs have foundered. Yet *Wands* exemplifies that

inoperative embodiments, even if they outnumber operative embodiments, do not rise to undue experimentation. Furthermore the citation of experimentation on drugs that foundered is evidence that such experimentation is in fact routine, not undue. The Office Action fails to make a case that experimentation required to practice the claimed invention would be considered undue. This factor fails to support a *Wands* based rejection.

(4) State of the Prior Art. The Examiner states that he is unaware of art that might render piperidinyl amino purines obvious or anticipated when used as anticancer agents as featured in the instant claims. Merely because similar compounds may not have successfully achieved any arbitrary task cannot be taken as indicative that undue experimentation would be required in the present context. This factor is yet another that fails to support a *Wands* based rejection.

(5) Working Examples. The Office Action alleges a lack of working examples in treating any specific disease. The Office Action further alleges that despite evidence of modulating CDK activity as shown in TABLE 2, the noted effects cannot be generalized to other CDKs. While not commenting in detail on the extent of generalizing one might accurately make, Applicants respectfully submit that for any, CDKs unaffected by one or more of the instant compounds, only routine, not undue experimentation would be required to identify inoperative embodiments. *Wands* is instructive that when even a majority of embodiments are inoperative, the experimentation is presumed to be undue. *Atlas Powder* 750 F.2d 1569, 1576-77 (CAFC 1984), a pre-*Wands* case) supports this reasoning:

> We agree with the district court's conclusion on enablement. **Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid.** "It is not a function of the claims to specifically exclude ··· possible inoperative substances···" *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted). *Accord*, *In re Geerdes*, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *In re Anderson*, 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1973). Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. *See, e.g.*, *In re Cook*, 439 F.2d 730, 735, 58 CCPA 1049, 169 USPQ 298, 302 (1971). That, however, has not been shown to be the case here. [Bolding added.]

Similarly, there is no showing in this case that one of ordinary skill in the art would be required to experiment unduly to identify possible CDKs that might be refractory and thus represent inoperative embodiments. Once again, analysis of this factor mitigates against a *Wands* based rejection.

(6) Skill of those in the art. Applicants believe that the quotation at the bottom of page 27 summarizes this rejection. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally." This goes to the issue

of anticipation or obviousness. The issue with respect to this rejection is not whether the present compounds are a revolutionary exception, rather the issue is the amount of experimentation; does it rise to the level of undue? As discussed in (5) above, inoperative embodiments are tolerated. The issue is not whether or not one or more inoperative embodiments might exist. Rather, the issue is the quality and quantity of experimentation required. The Office Action has made no showing that any experimentation that might be required to practice the present invention would be considered undue. Analysis of this *Wands* factor does not support a 35 U.S.C. §112 enablement rejection.

Similarly, the Office Action covers several pages describing nuanced differences in autoimmune disease. Differing mechanisms are cited. Yet unifying features such as cellular proliferation are ignored. While some autoimmune diseases require cytokinesis, others may not. But they all require proliferation of cells to effect the disease state. A tool or compound that takes advantage of the similarities for effect need not specifically affect each difference that might be cited. The Office Action ignores the issue that for an enablement rejection to be deemed proper, a *prima facie* case that undue experimentation and not just routine experimentation would be required must be established. The Office Action fails in this regard.

As discussed above, in introducing this rejection, undue experimentation is the test used to determine enablement. The Office Action fails to appreciate the case law surrounding enablement, in this particular instance, the issue of non-working or inoperative embodiments. Applicants trust that the discussion above adequately addresses this issue.

Later in the same paragraph, the Office Action makes note that the specification fails to teach what is known in the art, for example, with respect to B-cells (a cell type mentioned in the previous November 17, 2005 Office Action). Applicants respectfully submit that no nexus has been shown relating to whether the instant specification mentions B-cells specifically and how this might assist one to conclude that undue experimentation might be required to practice the instant invention. Thus, this discussion in the Office Action fails to support the 35 U.S.C. §112, first paragraph, enablement rejection.

The remainder of the section relating the 35 U.S.C. §112, first paragraph, enablement rejection similarly avoids the issue of the level and quality of experimentation, for example, whether routine or undue experimentation might be implicated. Differences in various embodiments, without more, do not support a conclusion that undue experimentation would be required. Issues relating anticipation and obviousness to a 35 U.S.C. §112, first paragraph, enablement rejection are discussed above and not repeated here.

In summary, while the Office Action has covered many pages with discussions of diseases and successful and failed treatments, nowhere is the quantity and quality of experimentation shown to be undue. In the absence of such *prima facie* showing, this rejection cannot be deemed proper. Reconsideration and withdrawal of this rejection are respectfully requested.

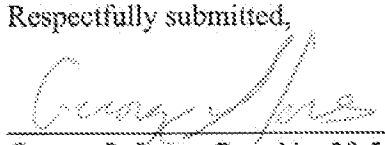
Double Patenting

Applicants gratefully acknowledge the Examiner's indication of a double patenting issue. However, since no claims are deemed allowable, the final form and number of the claims that might issue in this application is unknown. A terminal disclaimer at this time is premature as any claim(s) that might issue may or may not be deemed obvious over claims 1-10 of USP 6,861,524.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt indication of such. Should the Examiner wish to suggest additional amendments that might place the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below. Applicants are prepared to file a Terminal Disclaimer to effect immediate issuance of a Notice of Allowance if the Examiner indicates allowability of claims to which such Disclaimer would apply.

Respectfully submitted,



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